SUMMARY OF NEW AWARDS
BIOENGINEERING RESEARCH PARTNERSHIPS (BRP)
FY 2003

Grant:	1R01CA085139-01A2	
Principal Investigator:	CHIOCCA, E. A	MD
Title:	Interdisciplinary Tumor Complexity Modeling	
Institution:	MASSACHUSETTS GENERAL HOSPITAL	BOSTON, MA
Project Period:	2003/09/10-2007/07/31	

DESCRIPTION (provided by applicant): "Interdisciplinary Tumor Complexity Modeling". In spite of aggressive l therapies, the outcome for patients suffering from highly malignant brain tumors remains uniformly fatal. Responsible for this grim outcome are rapid tumor growth, clonal heterogeneity, acquired treatment resistance and extensive tumor invasion, rendering cytoreductive therapy ineffective. We believe that malignant tumors behave as complex dynamic, adaptive and self-organizing biosystems rather than as unorganized cell masses. If this is true, such malignant tumors also have to be investigated and ultimately targeted as complex: systems. Our work is therefore motivated by the following three hypotheses: (1) malignant brain tumors behave as complex dynamic biosystems; (2) these tumors systems invade according to the principle of "least resistance, most permission and highest attraction "; (3) their spatio-temporal behavior can be studied, simulated and predicted using an interdisciplinary approach combining in vitro and in vivo experiments, human imaging data and computational modeling. To investigate these hypotheses, our specific aims are as follows. Specific AIM 1: We will develop a novel 3D in vitro assay system, suitable of displaying several key-features of multicellular tumor spheroids (MTS) in parallel over a prolonged period of time. The experimental studies using these devices include the microstructural analysis of the extracellular matrix gel-medium as well as the structural, genetics and functional analysis of the spatio-temporal expansion of the micro-tumor system (i.e., on site proliferation and invasive cell network). We will also study tumor growth, invasion and physiology (blood flow and blood volume) in vivo, using MR-imaging of an orthotopic xenogeneic brain tumor model in athymic rats. Studies follow, which investigate invasive tumor cell dynamics in vivo with and without specifically implanted "attractor" sites. Both, in vitro and in vivo results will generate dynamic, multiscaled multi-modality data sets, which will then be incorporated into the computational models. Specific AIM 2: We will develop a set of related, innovative computational models to simulate brain tumor proliferation, genetic and epigenetic heterogeneity, angiogenesis and most importantly, tissue invasion. Discrete and continuum approaches include a variety of techniques such as cellular automata, Kinetic Monte Carlo (KMC) simulations, agent based modeling, gene-regulatory net modeling, fractal analysis and coupled reaction-diffusion equations. Once developed, the computational models will drive the experiments and vice versa. Finally, the merged models will be used to predict the course of brain tumor expansion using real human imaging data (retrospective study) and will be further developed into powerful virtual reality platforms for treatment planning and surgical training tools (feasibility study). Based on our convincing preliminary studies paradigm-shifting insights into brain tumor growth, heterogeneity, invasion and angiogenesis can be expected. The presented work is highly innovative and profoundly interdisciplinary as it combines many seemingly disparate disciplines such as cancer research, statistical physics and mechanics, materials science, biomedical engineering and -imaging, computational visualization, mathematical biology, computational and complex systems science. This Bioengineering Research Partnership investigates groundbreaking tumor biology concepts. This work can therefore very well build the basis for the development of novel diagnostic tools, innovative patient specific treatment planning devices and thus, may ultimately lead to more successful therapeutic strategies, capable of changing the grim outcome of the many patients suffering from this devastating disease.

Grant:	1R01CA096483-01A1	
Principal Investigator:	CLARKE, ROBERT	
Title:	Molecular Analysis of Human Breast Cancer	
Institution:	GEORGETOWN UNIVERSITY	WASHINGTON, DC
Project Period:	2003/09/12-2008/07/31	

DESCRIPTION (provided by applicant): Many women with small, node-negative breast cancers are essentially overtreated. For example, most Stage I breast cancers are treated with both local and systemic therapies but approximately 80% are effectively cured with local interventions alone. Separating these patients from the approximately 20% who recur, irrespective of their treatment, remains problematic. Consequently, the development of novel methods that can more accurately predict for a nonrecurrent vs. recurrent phenotype is a major priority. We address this issue in our response to PAR-02-010, for which we have established an imaginative and integrated Bioengineering Research Partnership comprising three research teams (Bioengineering & Biostatistics; Clinical & Pathology; Microarray & Molecular Analysis) from two local sister universities (Georgetown University and The Catholic University of America) and the University of Edinburgh (Scotland). We will apply expression microarray and tissue array technologies and powerful new data analysis algorithms to define the gene expression profiles of 600 invasive breast tumors (Stages I-III). Our multidisciplinary teams will use these molecular profiles and established prognostic factors to build artificial intelligence-based classifiers and multivariate models that accurately predict those patients with nonmetastatic disease (especially Stage I) who will not recur. In the long terms, the genes in this classifier and the classifier's algorithms will be used to build custom diagnostic arrays and software for routine clinical use. HYPOTHESES: We hypothesize that differences in the gene expression profiles of tumors determine outcome (recurrence) in patients with nonmetastatic disease. We also hypothesize that computational bioinformatics can discover these differences and use this knowledge to build classifiers that predict each patient's prognosis (especially in Stage I disease). AIM 1: We will perform gene expression analysis on breast needle biopsies of 600 invasive, nonmetastatic breast tumors. AIM 2: We will build an integrated data processing and management system for data acquisition and retrieval, to support the data analysis algorithms to be optimized and applied in Aim 3. AIM 3: We will optimize and apply novel pattern recognition and information visualization technologies, recognizing the high dimensional nature of the data, to discover and validate gene subsets that separate recurrent from nonrecurrent tumors. We will integrate advanced artificial intelligence algorithms and biostatistical models to build predictive classifiers that can more accurately define cancer phenotypes and predict clinical outcomes. AIM 4: We will use tissue arrays (multiple cores from archival tissues arrayed on glass slides) to validate and optimize the performance of these classifiers in a retrospective prognostic study of human breast tumors.

Grant:	1R01HL073647-01	
Principal Investigator:	DEL NIDO, PEDRO J	
Title:	Image-guided Intracardiac Beating Heart Surgery	
Institution:	CHILDREN'S HOSPITAL (BOSTON)	BOSTON, MA
Project Period:	2003/07/15-2008/06/30	

DESCRIPTION (provided by applicant): Modem cardiac surgical practice involves the routine use of cardiopulmonary bypass (CPB) for performing both coronary artery bypass graft (CABG) procedures on the heart surface as well as procedures inside the heart, classified broadly as intracardiac surgery. However, recent studies indicate that CPB carries important risks that can lead to reduced neuropsychiatric function and stroke in adults, and neurodevelopmental deficits with impaired fine motor skills in children. Other adverse effects of CPB include activation of inflammatory mediators and the complement cascade, showers of particulate emboli with aortic manipulation and crossclamp release, and air embolus. To avoid these risks of CPB, several investigators have begun to evaluate the results of CABG procedures performed without CPB. Early results of these "beating heart" procedures indicate equivalent patency rates, comparable mortality rates, and significant savings. Development of techniques for intracardiac beating heart surgery, however, must overcome the unique challenge of the inability to image the anatomic features of the heart with sufficient detail and time resolution to permit instrument navigation and precise tissue manipulation. Real time 3D echo has the potential for overcoming these issues thereby enabling intracardiac beating heart surgery. The overall aim of this proposal is to adapt real time 3-D ultrasound imaging specifically for image-guided interventions and integrate this technology with safety measures through instrument tracking, tactile sensing, and acoustic tissue analysis to permit safe and accurate intracardiac beating heart surgery. The complexity of this problem is well suited to a BRP approach. The PI has assembled a multidisciplinary team and established a unique partnership among industry-based engineers (Philips Medical Systems), university-based engineers (Harvard University; Boston University), and clinical investigators (Children's Hospital; Brigham and Women's Hospital). Together, we will approach this problem by addressing the following specific aims: AIM I: Modify real-time 3-D ultrasound to optimize image presentation for guiding intracardiac surgical procedures in a beating heart. AIM II: Adapt high-resolution electromagnetic tracking equipment for precise intracardiac navigation and modify surgical instruments to limit interference with ultrasound imaging during beating heart surgical procedures. AIM III: Develop instruments to provide both tactile sensing and acoustic tissue analysis for increased procedure safety. AIM IV: Integrate real time 3-D ultrasound imaging and tracking equipment with computer-enhanced instrument control for improved task performance and safety during image-guided surgery.

Grant:	1R01CA097966-01	
Principal Investigator:	FELD, MICHAEL S	PHD
Title:	Spectroscopic imaging and diagnosis of neoplasia	
Institution:	MASSACHUSETTS INSTITUTE OF TECHNOLOGY	CAMBRIDGE, MA
Project Period:	2003/08/15-2008/07/31	

DESCRIPTION (provided by applicant): This is a proposal to the National Institutes of Health to establish a Bioengineering Research Partnership to develop a spectroscopic imaging methodology for diagnosing pre-invasive neoplasia (dysplasia) and monitoring its progression. The proposed program is based on optical spectroscopic clinical instrumentation and associated diagnostic algorithms successfully developed at the MIT Spectroscopy Laboratory. The instrument to be developed will have two components, a system for wide-area imaging of neoplasia, based on light scattering spectroscopy i(LSS), and an optical fiber probe device for studying suspect regions thus revealed, based on tri-modal spectroscopy i(TMS). The goal of the program is to develop and perfect the new technology and assess its application to the diagnosis, characterization, and therapy of neoplastic progression in human patients in real time, The detection and monitoring of neoplastic lesions in the oral cavity and the cervix will be used as model systems for establishing the potential of the technology. In addition, basic studies to further improve the technology and its ability to characterize pre-invasive neoplasia will be conducted. Six projects will be undertaken, each led by an experienced investigator: (I) Prototype instruments and diagnostic algorithms for clinical studies will be developed, maintained and perfected. Clinical studies will be conducted on patients with suspected lesions in the (2) oral cavity and (3) uterine cervix to evaluate and perfect the technology for diagnosing and monitoring dysplasia and predicting the patient's response to chemopreventive and immunotherapeutic agents. Two basic projects aimed at enhancing the diagnostic accuracy of the clinical instrumentation will be undertaken, one (4) to explore the use of quasi-multiple scattered light to enhance the sensitivity and provide depth resolution to LSS imaging, and a second (5) to develop novel spectroscopic end-points based on well-characterized molecular and cellular events associated with the progression and regression of disease. (6) Pathology support activities will include analysis of oral and cervical tissues for molecular markers, and analysis of histologic sections of the same biopsy tissue by computer-assisted quantitative image analysis. An administrative core will coordinate the multidisciplinary activities of the program and insure information sharing and efficient communication. The partnership, composed of expert investigators at six institutions, will include experienced bioengineers with training in physics and mechanical/electrical engineering, pathologists experienced in cancer research, and hospital-based clinicians specializing in oral and cervical dysplasia.

Grant:	2R01HL058582-04A1	
Principal Investigator:	FRENCH, BRENT A	PHD
Title:	GENE THERAPY FOR MYOCARDIAL STUNNING AND INFARCTION	
Institution:	UNIVERSITY OF VIRGINIA CHARLOTTESVILLE	CHARLOTTESVILLE, VA
Project Period:	1997/09/01-2007/05/31	

DESCRIPTION (provided by applicant): Contractile dysfunction early after large myocardial infarction (MI) is not limited to necrotic tissue, but extends also to non-ischemic zones of the left ventricle (LV) remote from the ischemic region. We hypothesize that reactive oxygen species (ROS) and pro-inflammatory cytokines and elaborated by leukocytes infiltrating the heart after reperfused MI play a key role in the pathophysiology of this reversible form of LV dysfunction. We propose that whole-animal experiments employing a complementary set of pharmacologic and genetic approaches will help to elucidate the role of inflammatory activation in remote zone LV dysfunction post-MI and to identify effective treatment strategies for preserving LV function after large MI. In preliminary studies, our partnership has developed a mouse model of remote zone LV dysfunction after reperfused MI and has validated it using cardiac magnetic resonance imaging (MRI). Using MRI in combination with molecular techniques, the functions of oxidative stress, TNF-alpha, NF-kappaB, and iNOS will be evaluated using specific pharmacologic agents and genetically manipulated mice. A multidisciplinary approach will be used that encompasses the fields of biomedical engineering, radiology, cardiovascular physiology, pharmacology, immunopathology, cell biology and molecular genetics. The specific aims are to: 1) Validate a novel cardiac MRI pulse sequence and use it to define the time course of remote zone LV dysfunction in mice. While our preliminary MRI studies show that remote LV dysfunction resolves within 7 days after MI, we propose to apply a newly-developed CSPAMM-based DENSE pulse sequence to assess regional contractile function at even higher resolution. 2) Probe the pathophysiology of remote zone LV dysfunction post-MI using a pharmacologic approach. We hypothesize that pharmacologic agents capable of controlling oxidant stress, blocking TNF-a, inhibiting NF-?B and/or suppressing iNOS will preserve contractile function in remote, non-infarcted regions of the LV after large MI. 3) Probe the pathophysiology of remote zone LV dysfunction post-MI using genetic approaches. In preliminary studies, we have shown that contractile function in the remote LV is preserved in iNOS knock-out mice after large MI. Similarly, we hypothesize that remote LV function after MI will be preserved in TNF-a knock-outs, in mice with impaired NF-?B signaling, and in transgenic mice overexpressing SOD. Gene therapy with an Ad5 vector expressing SOD should yield similar results. 4) Determine the role of hematopoietic cells in remote zone LV dysfunction using bone marrow chimeras. We hypothesize that the beneficial effects of the genetic interventions investigated in Aim 3 may not depend entirely on hematopoietic cells, and propose a series of bone marrow transplantation experiments with iNOS knock-out mice to address this possibility.

Grant:	1R01EY013516-01A1	
Principal Investigator:	HUANG, DAVID	
Title:	Advanced Imaging for Glaucoma	
Institution:	CLEVELAND CLINIC LERNER COL/MED-CWRU	CLEVELAND, OH
Project Period:	2003/09/30-2004/08/31	

DESCRIPTION (provided by applicant): Glaucoma is a leading cause of blindness that presents a considerable diagnostic challenge. Studies have shown that, in glaucoma, up to half of the retinal nerve fibers can be lost before detection. Our goal is to improve glaucoma diagnosis with new imaging methods that can reveal tissue and cell-level structures in the retinal layers affected by glaucoma. These methods are optical coherence tomography (OCT) and light scattering spectroscopy (LSS). OCT is a novel technology that provides cross-sectional retinal images with micron level resolution, which is not possible with any other non-invasive method. It has been used to measure the peripapillary retinal nerve fiber layer (NFL) thickness. Although NFL thickness correlates well with conventional diagnostic indicators, there is still considerable overlap between glaucomatous and normal eyes. We propose to go beyond NFL thickness measurements and develop OCT -based technology to measure internal NFL properties such as reflectivity, birefringence, and backscattering angular distribution. We will also develop high-speed and ultrahigh resolution OCT to allow direct measurement of the much thinner ganglion cell layer (GCL). LSS can detect the sizes of even finer structures such as cell nuclei by measuring resonant spectral modulation in backscattered light. We propose to use LSS to detect glaucomatous changes in sizes of structural components in the GCL and NFL. Cleveland Clinic Foundation, the lead institution, will build these advanced imaging systems using technologies to be developed at Duke Univ., Case Western Reserve Univ., and Harvard Medical School. Initial instrument validation will use animal models of glaucoma developed at CCF and Bascom Palmer Eye Institute (BPEI). The new instruments will be tested in a 5-year clinical trial at CCF, New England Eye Center, and BPEI. High speed OCT will be used in year 1 with other technologies to be introduced to the clinical trial in years 2-4. The greatest portion of the trial will assess the ability of advanced imaging to predict which ocular hypertensive patients will later develop glaucoma as defined by conventional visual field and optic disc evaluation. If these advanced imaging technologies can predict glaucoma development, then they may allow earlier treatment and prevention of visual loss.

Grant:	1R01EB001659-01	
Principal Investigator:	MARK, ROGER G	MD
Title:	Integrating Data, Models, and Reasoning in Critical Care	
Institution:	MASSACHUSETTS INSTITUTE OF TECHNOLOGY	CAMBRIDGE, MA
Project Period:	2003/09/30-2008/07/31	

DESCRIPTION (provided by applicant): The objective of this Bioengineering Research Partnership is to focus the resources of a powerful interdisciplinary team from academia (MIT), industry (Philips Medical Systems), and clinical medicine (Beth Israel Deaconess Medical Center, BIDMC) to develop and evaluate advanced ICU patient monitoring systems that will substantially improve the efficiency, accuracy, and timeliness of clinical decision making in intensive care. Modern intensive care units employ an impressive array of technologically sophisticated instrumentation to provide detailed measurements of the pathophysiological state of each patient. In the long term, we plan to build monitoring systems that not only report these measurements to human users but also form pathophysiological hypotheses that best explain the rich and complex volume of relevant data from clinical observations, bedside monitors, mechanical ventilators and a wide variety of laboratory tests and imaging studies. Such systems should reduce the ever-growing problem of information overload, and provide much more accurate and timely alarms than today's unintegrated limit alarms. By helping to focus the practitioner's attention on the most significant events and changes in the patient's state and by suggesting likely physiological interpretations of that state, such systems will eventually permit early detection of even complex problems and provide useful guidance on therapeutic interventions; thus their use should lead to improved patient outcomes. To achieve these long-term goals, we propose a step-wise approach. First, we will create a research database of 500 data-rich ICU cases that we will de-identify and thoroughly annotate so that we can make it available as a resource for ourselves and other researchers. Second, we will develop an array of sophisticated model-based and reasoning methods and corresponding software to analyze the data we collect and to create the technical means of abstracting from detailed data to pathophysiological hypotheses. Third, we will evaluate the utility of our newly developed tools in the laboratory utilizing the new database. Finally, we will deploy the most successful of our new techniques into clinical practice in the BIDMC ICUs to compare their safety and efficacy with existing monitoring systems.

Grant:	1R01HL070537-01A1	
Principal Investigator:	MC INTIRE, LARRY V	
Title:	Leukocyte Trafficking: From Flow Blood to Tissue	
Institution:	GEORGIA INSTITUTE OF TECHNOLOGY	ATLANTA, GA
Project Period:	2003/09/29-2008/08/31	

DESCRIPTION (provided by applicant): This Bioengineering Research Partnership proposal combines expertise from the Bioengineering Department at Rice University and the Section of Leukocyte Biology from Baylor College of Medicine to examine the detailed sequential processes involved in movement of leukocytes from flowing blood to migration in tissues. A systems approach is presented, with the goal of identifying the crucial molecular mechanisms involved at each step and then integration of the steps as would occur in vivo. Both in vitro and in vivo (principally mice) models will be employed - the former to test specific molecular hypotheses and the latter to ensure that mechanisms identified in vitro are of importance in the actual in vivo setting. Three specific aims are proposed Specific Aim 1 The study of the effects of fluid shear and the interactions of leukocytes and endothelial cells on adherent leukocytes. This aim will use cone-plate viscometry and parallel plate flow systems to investigate the influence of shear on secretory functions and phenotypic changes in adherent neutrophils Specific Aim 2. The study of the interactions of leukocytes and endothelial cells under shear conditions and the effects on vascular permeability. This aim will use both in vitro and in vivo experimental models to investigate the sites of neutrophil adhesion and transmigration, and changes in endothelial and vascular permeability Specific Aim 3. The study of the mechanisms of leukocyte migration through extracellular matrix, and the phenotypic changes induced by the processes required for transendothelial migration. This aim will utilize a synthetic mimetic of extracellular matrix to investigate the contributions of proteolysis, adhesion and haptotaxis in vitro, and intravital microscopy to investigate migration through extracellular matrix in vivo. Basic bioengineering expertise is crucial for the success of each Specific Aim and for the integration of aims - involving aspects of biomechanics, transport phenomena, complex biological systems, cellular engineering and biomaterials. We believe the results of these interdisciplinary studies, combining quantitative bioengineering models, novel biomaterials, basic leukocyte biology and fundamental vascular biology will lead to significant advances in our understanding of leukocyte trafficking, with important implications in both normal physiology and various pathological states.

Grant:	1R01AR048776-01A1	
Principal Investigator:	MIJAILOVICH, SRBOLJUB M	BS
Title:	Bioengineering Analysis of Muscle Mechanics & Metabolism	
Institution:	HARVARD UNIVERSITY (SCH OF PUBLIC HLTH)	BOSTON, MA
Project Period:	2003/09/01-2008/04/30	

DESCRIPTION (provided by applicant): Using the methods of engineering analysis, we will develop a computational platform that incorporates current knowledge of molecular structure, biochemical energetics, and contraction kinetics to describe muscle contraction. Our goal is to develop a comprehensive model that can be used to (1) generate new mechanistic hypotheses concerning the functions of the contractile proteins myosin and actin and (2) quantitatively evaluate the roles of accessory and regulatory proteins in contraction. Once developed, the model will be a powerful analytical and predictive tool in studies of muscle contraction. Presently, no models of contraction account for complications due to both (1) extensibility of the actin and myosin filaments and (2) Ca^{2+} regulation of contraction. Filament extensibility results in non-uniform load transfer along the thick and thin filaments, which introduces variability in the stress and strain of the myosin heads during their interactions with actin. These effects must be taken into account to understand how cross-bridge forces affect chemical transitions in the actomyosin ATPase cycle and vice versa. Further, quantitative understanding of Ca^{2+} regulation will allow (1) more accurate predictions of the macroscopic mechanical and energetic consequences of specific regulatory events and (2) more accurate explanations of macroscopic events in terms of underlying molecular processes. This BRP addresses these problems via a multidisciplinary approach that spans engineering science, computational science, and biophysics and rests entirely upon first principles. Our team will develop a model of contraction that integrates a critical missing element-filament extensibility-with recent advances in understanding the (1) biochemical states of myosin; (2) transitional rate constants in the actomyosin ATP hydrolysis cycle; (3) function of myosin molecular motors in the thick and thin filament lattice (sarcomere); and (4) Ca 2+ regulation of myosin binding. Initially, the model will combine probabilistic or stochastic actomyosin binding kinetics with finite element analysis (either continuous or spatially discrete consistent with the periodicities of the thick and thin filaments). The model will then be refined to explain smooth muscle contraction, including the energetically efficient latch state and the actions of proteins involved in the regulation of contraction. The computational model developed here will invoke unifying principles that apply to the actomyosin interaction cycle regardless of muscle type but will have sufficient flexibility to account for contraction kinetics and regulation of contraction in different muscle types. Quantitative modeling of contraction is ultimately essential for understanding the molecular basis for a wide range of syndromes and diseases, such as airway narrowing in asthma and weakness of both heart and skeletal muscles in heart failure.

Grant:	1R01DC005762-01A1	
Principal Investigator:	MILES, RONALD N	PHD
Title:	Sensing and Processing for Directional Hearing Aids	
Institution:	STATE UNIVERSITY NEW YORK BINGHAMTON	BINGHAMTON, NY
Project Period:	2003/09/26-2007/08/31	

DESCRIPTION (provided by applicant): The aim of the proposed effort is to develop revolutionary technology for hearing aids that will lead to a marked improvement in the ability of the hearing impaired to understand speech in noisy environments. Our focus is on improving the technology of acoustic sensing and processing of signals so as to minimize the influence of unwanted sounds. We will accomplish this by a highly coordinated team effort to ensure that the design parameters of each feature of the system are mutually optimized and are compatible. This effort may be viewed as having three closely interrelated areas of technology development: novel directional microphones, novel optical electronic readout, and novel signal processing.

Grant:	1R01HL073632-01	
Principal Investigator:	PATZ, SAMUEL	PHD
Title:	Infrastructure and Applications of Hyperpolarized 129Xe	
Institution:	BRIGHAM AND WOMEN'S HOSPITAL	BOSTON, MA
Project Period:	2003/08/01-2007/07/31	

DESCRIPTION (provided by applicant): The field of 3He hyperpolarized gas MRI has seen great advances recently. This is not the case for MRI with 129Xe gas. The principal reason for this disparity is the limited supply of highly polarized 129Xe gas available for studies. For example, present day polarization apparatus for 129Xe MRI typically provide less than 1/2 liter per hour at 10% polarization. Members of our collaboration have recently demonstrated a revolutionary new polarization apparatus that operates at lower xenon pressures and higher flow velocities than existing state-of-the-art. Their results have confirmed that higher xenon polarizations can be obtained at lower operating pressures with fixed gas production rate. Thus the purpose of this BRP is to use this exciting new source of highly polarized and high throughput]29Xe gas to explore its potential to provide quantitative information on lung structure and function. While both 129Xe and 3He provide excellent ventilation maps, 129Xe is unique in 3 ways: (1) a high solubililty in tissue, (2) a large chemical shift of the tissue relative to the gas NMR frequency, and (3) a -25 times smaller diffusion constant compared to 3He. Properties 1 and 2 permit measurement of exchange of xenon gas into tissue. We will exploit this to determine the regional surface area to volume ratio, a microstructure parameter closely related to gas exchange efficiency. A second quantity, the diffusivity of 129Xe gas in the acinus, will also be measured as a function of the time allowed for diffusion to evolve. Because of Property 3, the short time 129Xe diffusion distance is smaller than possible with 3He, probing dimensions comparable to the average alveolar pore size. At long times, D(t) gives additional information about the lung microstructure, specifically the connectivity (or tortuosity) between adjacent acinar structures. Tortuosity may be an important predictor for susceptibility to airborne particulates. We propose measurements of 129Xe D(t) to establish its value as a "fingerprint" of lung microstructure. The team of researchers assembled for this proposal have been closely collaborating for over 6 years and have developed particular expertise in both polarizing and exploiting the unique features of 129Xe. A polarizer will be built, sited and supported at Brigham and Women's Hospital. Animal and human studies are proposed to demonstrate the structural and functional information 129Xe MRI can provide.

Grant:	1R01HL071635-01	
Principal Investigator:	PERTSOV, ARKADY M	PHD
Title:	3D Imaging of electrical activity in myocardial tissue	
Institution:	UPSTATE MEDICAL UNIVERSITY	ALBANY, NY
Project Period:	2003/05/01-2008/04/30	

DESCRIPTION (provided by applicant): Understanding the mechanisms that underlie abnormalities of electrical conduction in the heart is the key to the development of effective antiarrhythmic therapies. During the last decade, significant progress has been made in imaging electrical excitation waves in the heart using voltage-sensitive fluorescent dyes. However, until recently imaging using voltage-sensitive dyes was limited primarily to the epicardial surface. The goal of the proposed study is to develop a technology that would enable optical imaging of electrical excitation throughout the myocardial wall. Specifically, this technology should image the filaments, or organizing centers of vortex-like electrical activity. These are widely believed to be responsible for the initiation and maintenance of ventricular fibrillation, and the filaments are a key to their behavior. To address the technical challenges of this novel technology we propose a coordinated project involving the research groups of Dr. A. Pertsov (PI) from the Department of Pharmacology, SUNY Upstate Medical University, who pioneered the three-dimensional imaging of vortex-like excitation in chemical excitable systems and in the heart; Dr. D. Boas at the Harvard Medical School and the Massachusetts General Hospital NMR Center, an expert in optical tomography; Dr. L. Loew at the Center for Biomedical Imaging Technology, University of Connecticut Health Center (Co-PI), a leader in the development of voltage-sensitive probes and optical imaging; and the group of Dr. D. Weitz at the Department of Physics, Harvard University (Co-PI), renowned for their expertise in optical imaging and multiple-scattering media. The specific aims of the project are: 1) to create realistic computer models for reconstructing 2D optical images from 3D distributions of the transmembrane potential in myocardial tissue (forward problem), 2) to apply diffusive optical tomography to 3D reconstruction of the actual electrical activation in the heart (inverse problem); 3) to design, synthesize and test in myocardial tissues a family of near-infrared voltage-sensitive dyes optimized for 3D imaging of electrical activation in the heart; 4) to explore two-photon fluorescence and second-harmonic generation for 3D imaging of electrical activity in cardiac myocytes and tissues at subcellular and sub-millimeter scales. Successful completion of this project will break ground for a new technology, the 3D imaging of electrical activation in the heart.

Grant:	1R01HL069097-01A1	
Principal Investigator:	SALAMA, GUY	PHD
Title:	High-Speed, Depth-Resolved Images of Cardiac physiology	
Institution:	UNIVERSITY OF PITTSBURGH AT PITTSBURGH	PITTSBURGH, PA
Project Period:	2003/09/01-2008/08/31	

DESCRIPTION (provided by applicant): The long-term goal of this Bioengineering Research Partnership (BRP) is to develop a High-Speed, Depth-Resolved Imager (HSDRI) to map electrical activity or intracellular free Ca 2+ transients inside the myocardium of perfused hearts. The partnership consists of 3 groups. Dr. Guy Salama (PI at the University of Pittsburgh) will administer the BRP, develop the instrument and apply the new technology to problems in cardiac electrophysiology, that remain unresolved due to a lack of 3-D information. Drs. Alan Waggoner (at Carnegie-Mellon University, Director of the Center for Light Microscope Imaging and Biotechnology (CLMIB)) and Lauren Ernst will develop optical probes (voltage-sensitive and Ca2+ indicator dyes) with long excitation and emission wavelengths to improve tissue penetration and reduce light scattering from the myocardium. Dr. Fred Lanni (at CLMIB) will provide the theoretical and engineering expertise to develop and refine the HSDRI. The 3 groups will work in parallel. Aim 1 (Salama and Lanni, years 1-5): Two approaches will be developed and tested to obtain the best possible HSDRI system. (a) A system based on a Ronchi line grating to focus dark and bright bands in a focal plane 2-5 mm deep in ventricular tissue. Fluorescence images from the tissue will be taken (at 3k frames/s) during shifts of bright and dark bands of light excitation by 1/3 period. Images will be processed on-line to eliminate light emanating above and below the plane of focus to obtain depth-resolved images, at 1k frames/s. (b) A standard Nipkow spinning disk confocal imager will be modified for large fields-of-view (3x3 mm 2)and high frame rates. Aim 2 (years 1-5): Drs. Waggoner and Ernst will synthesize new longer wavelength fluorescent dyes to monitor action potentials (APs) or cytosolic free Ca2+(Cai) and Dr. Salama will test, analyze the spectral characteristics and response characteristics of the new probes in heart muscle. Aim 3 (Salama, Choi and Lanni years 1-5): Software will be developed to drive the HSDRI, analyze APs and Ca-i transients and map electrical activity in 3-D. Depth-resolved maps of activation, repolarization and AP durations will be used to investigate 2 topics in cardiac electrophysiology, where measurements in 3-D are essential to elucidate fundamental concepts. A) We will investigate the factors that modify electrical coupling (time-delay or block) between Purkinje fibers (P), Transitional (T) and Ventricular (V) cells to elucidate the role of PV junctions in the initiation and maintenance of arrhythmias. APs will be mapped in 3-D to resolve PV delays during antegrade and retrograde conduction, normoxic and ischemic in paced and during arrhythmias. B) Impulse propagation across the atrio-ventricular node (AVN) has been difficult to trace because of the complex 3-D structure of the node and the small region of compact cells. Activation maps of the AVN in 3-D will help us answer basic questions regarding the precise inputs to the node (fast and slow pathways), mechanisms of AVN reentry, Wenckebach periodicity and Wolf-Parkinson syndrome. Fast, depth-resolved images of voltage and Ca 2+are a powerful new tool that will have a wide range of applications in cardiac electrophysiology and can be extended to neuronal networks and other organ systems. We focus here on the heart because therein lie salient problems that are ready to be addressed by this new technology. However, the wide range of possible applications may lead to the commercialization of this new technology.

Grant:	1R01DE015633-01	
Principal Investigator:	TOMSIA, ANTONI P	PHD BIOENGINEERING / BIOMATERIALS
Title:	Complex Nanocomposites for Bone Regeneration	
Institution:	UNIVERSITY OF CALIF-LAWRENC BERKELEY LAB	BERKELEY, CA
Project Period:	2003/08/04-2008/05/31	

DESCRIPTION (provided by applicant): This Bioengineering Research Partnership proposal is submitted by a multidisciplinary collaboration of scientists primarily affiliated with the University of California (UC) system. The lead institution is Lawrence Berkeley National Laboratory, with component groups at UC Berkeley and San Francisco campuses. There is also small business collaborator from SkeleTech, Inc., in Bothell, WA. Some of the collaborators have worked together on ceramic projects for over 20 years, while others have worked together on dental research projects for over 10 years. This team has been expanded to include greater expertise in all the disciplines involved in this proposal: materials science, chemistry, biology, and dental/medical science. The research is aimed at development and testing of new implant materials by combining biomimetics with two radically new design philosophies to produce dense and strong bioactive scaffolds that are intended to be partially or completely resorbed and replaced by bone from the host in a sequence resembling bone remodeling. The ultimate goal is to develop strong and tough implant materials for load-bearing applications deriving their strength from nanoparticle hydroxyapatite and their toughness from hydrogel polymers, with the microstructural architecture scale on the order of tens of nanometers and below. Three types of materials will be developed. First, inorganic scaffolds with a dense core and a graded distribution of porosity and surface chemistry will be fabricated by stereolithography and by a novel technology developed in our laboratory based on freeze casting of calcium phosphate suspensions. Second, hydrogels and self-assembling polymers that possess anionic groups and adhesive ligands suitably positioned for the nucleation process and cellular adhesion will be used to direct templatedriven biomimetic mineralization of hydroxyapatite and other biominerals in nanoscopically and microscopically controlled fashion. Third, the resultant porous scaffolds will be used as the matrices to fabricate inorganic-organic composites with improved strength and fracture resistance. This will be achieved by infiltration of the inorganic scaffolds with hydrogels or by direct template-driven biomimetic mineralization of calcium phosphate nanoparticles on the organic scaffolds. Materials that pass the mechanical property tests will be tested in cell cultures and an animal model. Improvement of implants will result in improved health and quality of life for the millions of people who will need implants in the future.

Grant:	1R01HL071538-01	
Principal Investigator:	TRANQUILLO, ROBERT T	PHD
Title:	Tissue-engineering Valve from Cell-Remodeled Biopolymer	
Institution:	UNIVERSITY OF MINNESOTA TWIN CITIES	MINNEAPOLIS, MN
Project Period:	2003/06/01-2008/05/31	

DESCRIPTION (provided by applicant): This BRP aims to develop a tissue-engineered cardiovascular valve, with the initial focus being an aortic valve replacement. The "tissue-equivalent" approach to fabricating bioartificial tissues, in which a fibrillar biopolymer gel (type I collagen or fibrin) is contracted, aligned, and remodeled by entrapped tissue cells, will be used. A tissue mechanical theory will be applied to determine the optimal mold design such that cell-mediated compaction of the gel around the mold surfaces yields the target geometry and ECM fiber alignment. A coupled solid fluid mechanical model of valve function in pulsatile flow will be used to define what alignment-dependent mechanical properties of our "valve-equivalent" (VE)are desired following incubation for proper valve function, and to simulate what the VE function will be. Various experimental strategies will be implemented to manipulate these properties during incubation. High-speed ultrasonic imaging of leaflet motion will be developed and used along with particle imaging velicometry in order to validate the model as well as visualize valve function. In addition to comprehensive biological and biomechanical characterization of the VE, novel adult stem cells will be assessed as a source of endothelial cells and, potentially, interstitial leaflet cells for VE fabrication.

Grant:	1R01HL070542-01A1	
Principal Investigator:	TSUDA, AKIRA	PHD BIOMEDICAL ENGINEERING & MATH
Title:	Particles in Developing Lung: Bioengineering Approach	
Institution:	HARVARD UNIVERSITY (SCH OF PUBLIC HLTH)	BOSTON, MA
Project Period:	2003/09/15-2008/08/31	

DESCRIPTION: (provided by applicant): This bioengineering interdisciplinary partnership project plans to use engineering expertise to develop a combination of tools, including computational fluid mechanics, the development of particle technology, and physiological approaches in animal models, to be utilized in a comprehensive study on particle deposition, retention, and clearance pathways in the developing lung. There is no more important imperative in our society than to protect the health of children, yet the specific differences in pulmonary structure between newborn, children, and adult lungs have not been addressed in assessing health risks associated with environmental exposure to aerosol particulates. Children's lungs postnatally undergo remarkable structural changes, such as a dramatic increase in alveolation, in addition to an increase in size. Our recent studies clearly indicate that the structure of the acinar airways has a profound influence on fine particle deposition. It is, therefore, very likely that particle deposition, retention, and clearance pathways in infants and young children are significantly different from those in adults. In particular, our preliminary data suggest that health risks may rise rapidly postnatally and peak between 2 and 5 years. However, little is known about the qualitative and quantitative aspects of particle deposition in developing lungs, mostly because these questions are not accessible to clinical studies or experimentation for ethical and technical reasons. We propose: (1) to establish computational fluid mechanics methods and investigate the effects of structural changes during lung development on deposition; (2) to develop a state-of-the-art high precision lung function/inhalation detection methodology utilizing engineered tracer particles; and (3) to apply this new methodology to investigate how particles are deposited and retained in the postnatally developing rat animal model. These proposed studies will allow us, for the first time, to get a comprehensive picture of changes in particle deposition-retention associated with lung development. This knowledge has important implications for the estimation of health hazards posed by particulate air pollution and for the establishment of age-appropriate doses of therapeutic drugs delivered by aerosols.

Grant:	1R01HL069368-01A1	
Principal Investigator:	WAGNER, WILLIAM R	PHD
Title:	Cardiopulmonary Organ Engineering	
Institution:	UNIVERSITY OF PITTSBURGH AT PITTSBURGH	PITTSBURGH, PA
Project Period:	2003/07/01-2008/06/30	

DESCRIPTION (provided by applicant): The aim of this proposal is to design solutions for vascular, cardiac, and pulmonary organ failure by building interactive teams of researchers focused on specific aspects of cardiopulmonary organ engineering. Our efforts will encompass three projects: a tissue engineered blood vessel, a myocardial patch, and a biohybrid lung. The assembled research teams will function as cores of expertise that address common tasks associated with all three projects. Five research cores will be established in the following areas: 1) matrix synthesis and surface modification, 2) precursor cell isolation and characterization, 3) biomechanical testing and conditioning, 4) animal model development, and 5) construct assessment. For each of the three organ projects we have design objectives (Specific Aims) that will be achieved in the five-year period of proposed work: 1) Tissue engineered blood vessel - A biological blood vessel will be developed that achieves long-term potency in the rat model and is subsequently evaluated in the porcine model. The blood vessel will be a "biological equivalent" to autologous arteries from a mechanical and biofunctional perspective. During vessel development in vitro, specific mechanical training protocols that have been optimized to direct appropriate cell differentiation and expression of matrix components will be employed. 2) Myocardial patch - A process will be developed that allows the reconstruction of functional myocardium in ischemic or dysfunctional regions of the heart, This process will be characterized by the seeding of stem cells onto a bioerodible thermoplastic elastomer which has been designed to micromechanically transmit appropriate stresses to the stem cells during an in vitro seeding period and after placement within the diseased myocardium. Vascularization of this implanted construct will be achieved by surgical placement of omental tissue atop the placed myocardial patch. 3) Biohybrid lung - An oxygenator comprised of endothelialized microporous hollow fibers arranged in: plates and rotated to mix and pump the blood will serve as a biohyrid lung capable of providing gas exchange in a calf for 14 days. The hollow fibers will be surface modified to support the culture of autologous endothelial cells. The endothelial cells will act to reduce the anticoagulation requirements of the device while maintaining adequate fiber permeability.

Grant:	1R01DE014672-01A1	
Principal Investigator:	WAITE, JOHN H	
Title:	Biomimetic Blades: Mincing with Less Mineral	
Institution:	UNIVERSITY OF CALIFORNIA SANTA BARBARA	SANTA BARBARA, CA
Project Period:	2003/07/11-2006/05/31	

DESCRIPTION (provided by applicant): Tooth enamel and dentin are the premier materials in vertebrates for hardness and abrasion resistance. The superb properties of these materials are vital adaptations for proper ingestion nutrition and, when compromised through decay or injury, pose many fundamental and technical challenges to effective restoration. In polychaete worms such as Glycera and Nereis, the tooth-like jaws have a resistance to wear that is comparable to enamel; however, this is accomplished with a tenth as much mineralization (Glycera) or no mineralization at all (Nereis). We believe that these mainly proteinaceous jaws offer important insights into the design of biocompatible wear-resistant materials. Based on preliminary studies, we propose to demonstrate that specific proteins/polymers can be hardened and toughened by mineralization, metal ion chelation, or both. Our aim in this discovery-driven proposal is a state-of-the-art chemical, structural and mechanical characterization of the jaws using mass spectrometry, molecular biology, X-ray analysis and nanoindentation. Rigorous engineering principles will be applied to the analysis of jaws to distill a set of biomimetic rules regarding the relationship between structure and wear. Significant correlations between the chemical, microstructural and mechanical properties will be used to direct the preparation of His-containing copolymers into hard films containing Cu or Zn ions. The chief health benefits of this research will be insights about lightweight replacement materials with superior hardness and abrasion resistance.

Grant:	1R01NS046214-01	
Principal Investigator:	WANG, LIHONG	PHD
Title:	Functional brain imaging by laser-induced PAT	
Institution:	TEXAS ENGINEERING EXPERIMENT STATION	COLLEGE STATION, TX
Project Period:	2003/09/15-2008/07/31	

DESCRIPTION (provided by applicant): The objective of the proposed research is to develop a novel non-invasive laser-based technology for transcranial functional imaging of the brain of small animals in vivo. Small animals are the preferred laboratory models for studying various diseases, and small animal imaging provides the opportunity to evaluate pathologic progression in a much-compressed time frame and with a much-improved resolution. By combining high optical contrast and diffraction-limited high acoustic resolution, the proposed technology, functional photoacoustic tomography (fPAT), can image the intact brain free of speckle artifacts. Besides structural information, the proposed fPAT can also provide functional information including blood volume and blood oxygenation. In the proposed fPAT technology, a short-pulsed laser beam penetrates into the tissue sample diffusively. The photoacoustic waves, due to thermoelastic expansion resulting from a transient temperature rise on the order of 10 mK caused by the laser irradiation, are then measured around the sample by wide-band ultrasonic transducers. The acquired photoacoustic waves are used to reconstruct, at ultrasonic resolution, the optical absorption distribution that reveals optical contrast. Optical contrast is sensitive to the molecular conformation of biological tissue and is related to certain physiological parameters such as the level of hemoglobin oxygenation. The proposed fPAT technology combines the high-contrast advantage of optical imaging with the high 3D resolution advantage of ultrasound imaging. The proposed technology does not depend on ballistic/quasi-ballistic or backscattered light as optical coherence tomography (OCT) does. Any light, including both singly and multiply scattered photons, contributes to the imaging signal; as a result, the imaging depth in fPAT is better than in OCT. The resolution is diffraction-limited by the detected photoacoustic waves rather than by optical diffusion; consequently, the resolution of fPAT is excellent (60 microns, adjustable with ultrasonic frequency). Furthermore, fPAT is free of the speckle artifacts present in OCT and pulse-echo ultrasonography, two analogous technologies. The proposed research will be accomplished by a comprehensive multi-disciplinary team comprised of members of the Department of Biomedical Engineering at Texas A&M University (overall system), the Department of Pathobiology at Texas A&M University (animal experiments), the University of Connecticut (ultrasound system), the NIH Resource Center on Medical Ultrasonic Transducer Technology at the University of Southern California (ultrasound hardware), the University of Michigan (ultrasound software), and the National Institutes of Health (comparative study with fMRI/PET). The exciting aspect of this project is that the Texas A&M group has already successfully achieved high-quality in vivo PAT images of the rat brain. Because blood vessels of the brain are clearly imaged, this technology provides a unique opportunity to assess the functional parameters in a given blood vessel with a pinpoint accuracy. The applicants propose to advance this technology and explore its potential applications with the following specific aims: (1) Develop an ultrasound array system for rapid data acquisition and a single-wavelength photoacoustic tomography (PAT) system; (2) Develop a functional PAT (fPAT) system using a dual-wavelength laser system; (3) Image small-animal brain tumors using fPAT; (4) Image small-animal brain traumas using fPAT; (5) Image small-animal brain activation using fPAT; (6) Image small-animal brain chemotherapy using fPAT; and (7) Compare fPAT with established imaging modalities including fMRI/PET.

Grant:	1R01EB001672-01	
Principal Investigator:	WEIR, RICHARD F	PHD
Title:	Multifunction Prosthesis Control using Implanted Sensors	
Institution:	NORTHWESTERN UNIVERSITY	EVANSTON, IL
Project Period:	2003/09/30-2008/07/31	

DESCRIPTION (provided by applicant): The limitation of current prostheses is not the devices themselves but rather the lack of sufficient independent control sources. A system capable of reading intra muscular EMG signals would greatly increase the number control sources available for prosthesis control. Current state-of-the-art electric prosthetic hands are generally single DOF (opening/closing) devices often implemented with EMG control. Current prosthetic arms requiring multi-DOF control most often use sequential control. As currently implemented, sequential control is slow. We propose to develop a multichannel/multifunction prosthetic hand/arm controller system capable of receiving and processing signals from up to sixteen implanted bipolar differential electromyographic (EMG) electrodes. An external prosthesis controller will use fuzzy-logic to decipher user intent from telemetry sent over a transcutaneous magnetic link by the implanted electrodes. The same link will provide power for the implanted electrodes. . Northwestern University will develop the multifunctional prosthesis controller and perform the animal experiments necessary to demonstrate the implanted devices. . Rehabilitation Institute of Chicago will perform animal experiments and help with human subject experiments. . Illinois Institute of Technology will develop individually addressable integrated circuit EMG sensor packages. Each sensor will be housed in BION(r) hermetically sealed packages provided by the Alfred E. Mann Foundation. . Sigenics Corp. will develop the transcutaneous telemetry link, (or reader). A custom-designed application specific integrated circuit (ASIC) will "strip" the data from the link's telemetry and send it to the prosthesis controller. Powering of the implanted electrodes will also be controlled by the ASIC. The external coil of the inductive link will be laminated into a prosthetic socket. Development of each component of the system will occur in parallel. Throughout years 1 & 2 fine wire studies with human subjects will be used to develop multifunctional prosthesis control algorithms. Initial silicon for the implanted electrodes and reader ASIC will be ready by end of year 1. Packaged electrodes ready for animal testing and a prototype reader will be ready the middle of year 2. Year 3 is expected to be spent going through initial system integration and iterative test-redesign cycles. A definitive design is anticipated to be ready for final testing and tweaking by the middle of year 4. The final year will be spent conducting the final systems integration.

Grant:	1R01EY014743-01	
Principal Investigator:	WERNER, JOHN S	
Title:	Ophthalmic Imaging Using Adaptive Optics and OCT	
Institution:	UNIVERSITY OF CALIFORNIA DAVIS	DAVIS, CA
Project Period:	2003/09/30-2008/08/31	

DESCRIPTION (provided by applicant): The purpose of this BRP is to develop and evaluate new instrumentation that will permit unprecedented three dimensional imaging of single cells in the human retina, specifically rod and cone photoreceptors and ganglion cells. An interdisciplinary team will combine adaptive optics (AO), enabling the best lateral resolution for retinal imaging, with optical coherence tomography (OCT), providing the best axial resolution for retinal imaging. Two instruments will be developed using complementary OCT imaging modalities, flood illumination and enface scanning. These instruments will be used to study cellular morphology associated with normal aging, age-related macular degeneration (AMD) and glaucoma. The instruments will be compared quantitatively with each other and with existing retinal imaging devices. The project will be led by UC-Davis COCD), where a high-performance AO system has been developed in collaboration with the Lawrence Livermore National Laboratory (LLNL). This collaboration will be expanded to include a team of OCT experts at LLNL and Indiana University (IU). The IU team has previously collaborated with LLNL through the Center for Adaptive Optics and has already developed a working prototype AO-OCT system for retinal imaging. In this BRP project, LLNL will construct one AO-OCT instrument at the UCD site to be tested clinically in years 3-5, while the second AO-OCT instrument will be developed at IU in collaboration with LLNL and tested in the laboratory in years 4-5. Comparisons of AO-OCT and functional measures will be obtained at UCD and IU. Both instruments will be made available for use by scientists and clinicians who are not part of the BRP, and will be refined through the course of the project period. UCD has expertise in vision science, aging, and evaluation of AMD and glaucoma progression and treatment LLNL has a long history of research on AO for astronomy and has transferred some of its AO technology to vision science at UCD. LLNL also has expertise in OCT, and has pioneered its application to in vivo imaging of oral and vascular structures. The IU team has experience in AO-OCT and vision science with specific expertise in visual optics and retinal electrophysiology. This BRP is buttressed by consultants who have developed ophthalmic OCT technology at the University of Texas and Carl Zeiss Meditec. The Zeiss group has already transferred OCT technology to the clinic via commercial development and will facilitate incorporation of user friendly interfaces for our AO-OCT systems. This BRP thus combines the unique expertise of engineers, vision scientists and clinicians who have experience working together to effect a smooth transition from the laboratory to applications. This synergistic team will develop a new generation of instruments to advance vision science, permit retinal dysfunction to be studied in vivo in a way that will offer new insights into normal aging, the pathogenesis of glaucoma and macular degeneration, and a reliable method to monitor novel treatments for retinal disease.

Grant:	1R01EY014375-01	
Principal Investigator:	WILLIAMS, DAVID R	PHD PHYSIOL PSYCH
Title:	Optics Instrumentation for Advanced Ophthalmic Imaging	
Institution:	UNIVERSITY OF ROCHESTER	ROCHESTER, NY
Project Period:	2003/03/01-2008/02/28	

DESCRIPTION (provided by applicant): The two goals of this Bioengineering Research Partnership are (1) to design and construct a new generation of instruments for noninvasive imaging of the mammalian retina with 3-D resolution superior to existing technology and capable of resolving single cells in vivo. (2) to explore the value of this technology through application to human retinal disease and retinal surgery. These instruments will combine adaptive optics, a technology borrowed from astronomy that automatically corrects all the eye's aberrations, with confocal microscopy, a technology for optically sectioning the retina. The lead institution will be the University of Rochester, and partners include Lawrence Livermore National Laboratory, the Doheny Eye Institute at USC, the University of Houston, the University of California at Berkeley, and the Schepens Eye Research Institute. By the end of year 1, a device will be operational at each of four clinical sites: USC, Rochester, Houston, and Schepens. In years 2-5, these devices will provide high resolution imaging of neovascularization in age related macular degeneration and diabetic retinopathy, photoreceptors in retinal degenerative disease such as retinitis pigmentosa, ganglion cell bodies in glaucoma, individual retinal pigment epithelial cells, and blood flow in the smallest retinal capilliaries. In year 3, a new surgical microscope equipped with adaptive optics will be constructed by LLNL. Retinal surgeons at USC will evaluate this device in years 4-5. Based on its experience with earlier instruments, the BRP will design and build a sixth instrument in year 4 that will be portable, compact, and user friendly. This device will be available to investigators outside the BRP. The BRP brings together optical engineers, basic vision scientists, and clinical vision researchers. This will allow engineers to design instrumentation informed by the specific needs of clinical research, allowing them to translate adaptive optics technology directly into clinical application. LLNL brings to the partnership expertise in optical engineering and adaptive optics from the fields of astronomy and laser fusion. Rochester and Houston will contribute experience in adaptive optics applied to retinal imaging. Rochester first applied adaptive optics to high resolution retinal imaging and Houston has recently demonstrated a prototype adaptive optics system that is the precursor for the devices proposed here. Schepens brings international leadership in scanning laser ophthalmoscopy. UC Berkeley provides expertise in the study of retinal degenerative diseases. USC, with its innovative approaches to retinal disease and retinal surgery, will join Rochester, Houston, and Schepens in providing clinical sites for the evaluation of confocal adaptive optics technology.

Grant:	1R01CA091763-01A2	
Principal Investigator:	YU, YAN	PHD
Title:	Robot-Assisted Platform for Intratumoral Delivery	
Institution:	UNIVERSITY OF ROCHESTER	ROCHESTER, NY
Project Period:	2003/09/01-2008/08/31	

DESCRIPTION (provided by applicant): Intratumoral therapies of prostate cancer include the delivery of brachytherapy or ablation energy sources, and adenoviral injection, through a minimally invasive, transperineal approach. They require quantitative, optimized treatment planning, precise placement of the needles/probes according to the treatment plan, and real time dosimetric evaluation in the operating room as deviations from the treatment plan are detected. Recent studies suggest that imprecisions in standard brachytherapy using the manual technique cause higher than previously appreciated complication rates, and may be the cause of local failure in 15% of the patients. The major goal of the proposed work is to develop the Robot-Assisted Platform for Intratumoral Delivery (RAPID) for integrated treatment of prostate cancer, and to demonstrate the safety, efficacy and clinical effectiveness through bench/phantom tests and a Phase I clinical study. A number of maturing component technologies previously developed by the bioengineering research partners will be combined in this major collaboration, including the first robotic system for urological applications with early experience on actual patient treatment, the first treatment planning system with intraoperative dosimetry optimization, and the first needle/probe tracking system for real time ultrasound-based treatment verification, permitting re-planning and re-optimization of therapy delivery. The integrated RAPID system, designed based on prototype subsystems developed at each of the research partners, will initially focus on interstitial brachytherapy of prostate cancer. It is aimed at delivering precise, non-coplanar 3D conformal radiation rapidly and with assured consistency, and to incorporate such complex concurrent therapies as radiosensitization and mixed agent/strengths brachytherapy. Primary outcome variables including implant quality, cost, morbidity and learning curve will be examined under the clinical study by comparison with historical controls. The long-term objective of the RAPID project is to incorporate the delivery of concomitant therapeutic agents intratumorally for cancer in the prostate as well as in other organ systems. The multi-agent, multi-modality capabilities of the RAPID system will be continually exploited towards total optimization of a turnkey in vivo diagnosis and therapy engine for localized cancers of solid organs.